REMARKS

Applicant notes that the Examiner has renumbered claims 48-65 as claims 82-99, respectively. Applicant has amended the corresponding dependencies in claims 93 and 95-99. Applicant notes that the list of pending claims in the "Office Action Summary" erroneously omits claim 47. Applicant has not canceled claim 47, and page 2 of the Examiner's Office Action indicates that claim 47 is still pending and examined on the record. Office Action at 2. Claim 92 is hereby canceled. New claims 100-106 have been added. Thus, claims 4, 9, 13, 17, 21, 25-42, 44, 46-47, 82-91, and 93-106 will be pending upon entry of this reply. Claims 4, 9, 13, 26, 31-37, and 40 have been amended to clarify that which the Applicant regards as his invention. Support for new claims 100-101 can be found in the specification as filed at page 31, lines 26-27. Support for new claim 102 can be found in the specification as filed at page 34, lines 15-18. Support for new claims 103-104 can be found in the specification as filed at page 34, lines 18-21. Support for new claims 105-106 can be found in the specification as filed at page 34, lines 22-23. Support for the amendment to claims 4 and 13 can be found in the specification as filed at page 14, line 31. Additional support for the amendment to claim 13 can be found in the specification as filed at page 14, line 37 through page 15 line 1. Support for the amendment to claim 9 can be found in the specification as filed at page 17, lines 34-36. Support for the amendment to claims 26, 31-37, and 40 can be found in the specification as filed at page 9, lines 18-25. Applicant acknowledges the Examiner's withdrawal of the indefiniteness rejection of claim 44. Also acknowledged is the Examiner's withdrawal of the rejection of claims 26-31 as obvious over Chen *et al.*

THE ENABLEMENT REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 4, 9, 13, 17, 21, 25-42, 44, and 46-47, and now renumbered claims 82-91, and 93-99 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. While the Examiner acknowledges that "the specification has taught how to make and use a medicament for the treatment of cancer, wherein the medicament comprises a tumor or cancer related antigen in conjunction with HSP70, HSP90, and gp96" the Examiner maintains that the specification "has not taught how to prevent cancer." Office Action at 4. More specifically, the Examiner alleges that: 1) nowhere in the specification has it taught how to use the instant vaccine composition as a prophylactic composition so as to prevent the formation of cancer, the disclosure has only taught how to treat a pre-existing cancer; 2) the specification is devoid of studies, such as challenge studies, needed to establish a vaccine so as to prevent the formation of cancer; 3) the specification has not enabled the claimed methods with respect to any and all hsps; 4) there is no art of record that teaches which members of the population are to receive cancer treatments or prevention medicaments because it is not known which members of the population will develop cancer; and 5) the overactivated immune state may eventually lead to other diseases such as autoimmune disease.

Applicant sets forth the general legal standard for enablement and then addresses each of the Examiner's contentions in turn below.

THE LEGAL STANDARD

The test for enablement is whether one of skill in the art could make and use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). The specification preferably omits well

known subject matter. *See Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990)("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Accordingly, the law does not require the scope of enablement provided by the specification to mirror precisely the scope of protection sought by the claims. *See In re Fisher*, 166 USPQ 18, 24 (C.C.P.A. 1970); *see also In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). To be enabled, all the law requires is that the scope of enablement provided by the specification bear a "reasonable correlation" to the scope of the claims. *Id.* Moreover, even if evidence to doubt the proposed correlation exists, "the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Thus, to support a non-enablement rejection, the Examiner must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate the teaching in the specification across the entire scope of the claims. *Id.*

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369

(CCPA 1971); MPEP § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.*

THE SUBJECT MATTER OF THE CLAIMS
IS ENABLED FOR PROPHYLACTIC METHODS

Applicant respectfully asserts that no undue experimentation is required to prevent cancer in a subject through the co-administration of a cancer vaccine and an HSP preparation as set forth in the claims given the guidance provided in the instant specification and knowledge in the art. Moreover, the Examiner has not met his burden in presenting evidence that would lead a person of ordinary skill in the art to conclude that the present methods of treating and preventing cancer through the co-administration of a vaccine and an HSP preparation as set forth in the claims would require undue experimentation. Without conceding the correctness of the Examiner's rejection, Applicant has amended Claim 4, and thus all pending claims (via the remaining claims' dependencies), to reflect that the subject of the claimed method of treating or preventing cancer is a subject in need of said treating or preventing. Applicant believes the teachings contained in the specification would enable the skilled artisan to practice the claimed invention without any undue experimentation.

The specification provides detailed guidance to one of skill in the art seeking to carry out the methods of the invention. In particular, the specification teaches various vaccine compositions that can be used in the methods of the invention to prevent cancer, *e.g.*, vaccines containing tumor specific or tumor-associated antigens (specification at page 31, line 26), HSPs that may be used in the methods of the invention (specification at page 17, lines 34-36), methods of preparing and purifying HSPs and HSP complexes (specification at page 21, line 4 through page 31, line 11), patients (specification at page 32, lines 19-24),

dosages of HSP preparations (specification at page 34, lines 9-22), timing regimens (specification at page 34, lines 23-32), dosages of vaccine composition (specification at page 34 line 33 through page 35, line 5), considerations when selecting a site of administration (specification at page 35, lines 6-16), routes of administration (specification at page 35, line 17-26), buffers (page 35, lines 33- page 36, line 6), and formulations for numerous methods of administration (specification at page 36, lines 32 through page 37, line 35). The specification also sets forth numerous types of cancer that may be prevented by the instant methods (page 43, line 15 - page 44, line 4). The teachings provided therein would enable a skilled artisan to prevent cancer using the methods claimed herein without undue experimentation.

The specification provides guidance to one of skill in the art seeking to monitor the immune response elicited by the claimed methods. Specifically, the specification teaches one how to make a determination of the generation of immunogenic responses by administration of vaccines in conjunction with an HSP preparation. Specification at page 39, line 29. The assays described therein include ELISA assays, tetramer staining assays, mixed lymphocyte target culture assays, and ELISPOT assays. *See* specification at page 39, line 29 through page 42, line 37.

CHALLENGE STUDIES IN THE ART CONFIRM THE
ENABLEMENT OF THE PRESENTLY CLAIMED METHODS

Applicant respectfully directs the Examiner's attention to Reference BE (made of record in the revised form PTO-1449 filed on July 1, 2002), entitled "Exogenous heat shock proteins provide adjuvant effects on enhancing the immunogenicity of apoptotic tumor cells and inducing anti-tumor immunity," AACR 93rd Annual Meeting, April 6-10, 2002, Vol. 43, #2214, by H. Feng *et al.* ("Feng *et al.*").

Feng *et al.*, a post-filing date reference, corroborates the teachings of the instant specification. Feng *et al.* demonstrates preventative effectiveness. Feng *et al.* reports that 100% of mice immunized with a cancer vaccine (FasDD-induced apoptotic 12B1-D1 leukemia cells) combined with an HSP preparation which does not display the immunogenicity of the tumor (FS-IEFcc[1] from naïve mouse liver), that are subsequently challenged with a LD100 dose of tumor cells, reject the tumor challenge.

Applicant also respectfully directs the Examiner's attention to reference CP (made of record in revised form PTO-1449 filed on December 23, 2002), entitled "Exogenous stress proteins enhance the immunogenicity of apoptotic tumor cells and stimulate antitumor immunity" 2003, Blood 101(1): 245-252 by Feng *et al.* ("Feng II").

Feng II, a post-filing date reference, also corroborates the teachings of the instant specification. Feng II reports that mice injected with a cancer vaccine (AP20187-induced apoptotic 12B1-D1 tumor cells) combined with an HSP preparation which does not display the immunogenicity of the tumor (hsp70 devoid of tumor specific antigenic peptides) significantly delayed tumor growth compared with mice that were injected with the cancer vaccine (AP20187-induced apoptotic 12B1-D1 tumor cells) alone. See Feng II at page 247, first paragraph and Figure 1A.

Taken together, the results in Feng *et al.* and Feng II corroborate the teachings of the specification that HSP adjuvant vaccine therapy is prophylactically effective and useful. In sum, Feng *et al.* and Feng II corroborate the teachings of the specification that the administration of a vaccine composition that displays the immunogenicity of a component

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[1] Free solution/isoelectric focusing enriched multiple HSP (or chaperone complexes).

against which an immune response is desired in conjunction with an HSP that does not display the immunogenicity of the component would be useful in preventing cancer.

THE SUBJECT MATTER OF THE CLAIMS IS ENABLED FOR ANY AND ALL HSPS

The Examiner alleges that while the specification is enabling for methods of treating cancer using specific heat shock proteins, hsp70, hsp90, and gp96, the specification does not provide enablement for "any and all HSPs." Office Action at 4. Applicant respectfully submits that the broad scope of HSPs is enabled.

The Examiner has failed to meet his initial burden in proving non-enablement. The Examiner sets forth no reason of record to doubt the objective truth of the teachings in the specification. Even assuming *arguendo* that the Examiner has met his initial burden, Applicant asserts that the standard of reasonable correlation of enablement has been met in this case. Specifically, one of skill in the art would be able to practice readily the claimed methods using the hsps specifically taught in the specification, such as hsp70, hsp90, gp96, calreticulin, and grp94 (see specification at page 19, lines 16-27), as well as other hsps known in the art, *e.g.*, hsp110 and grp170. One of skill in the art reading the specification would be able to identify and/or make and use stress proteins in accordance with the methods of the invention.

Moreover, it has been shown that hsp110, grp170 and calreticulin, function like hsp70, hsp90, and gp96, in the immune system to promote immune response. When purified from tumor cells, these hsps bind antigenic peptides and elicit tumor immunity (see Wang *et al.*, 2001, *J. Immunol.* 165:490-497; reference CQ of the Supplemental Information Disclosure Statement and Basu *et al.*, 1999, *J. Exp. Med.* 189(5): 797-802; reference CR of the Supplemental Information Disclosure Statement). In addition, it has been shown that

calreticulin functions by the same mechanism as other stress proteins such as hsp70, hsp90, and gp96, by binding the same receptor CD91 on antigen-presenting cells (see Basu *et al.*, 2001, *Immunity* 14:303-313, made of record in revised form PTO-1449 filed on July 1, 2002 as reference AY).

The Examiner has presented no reason to doubt that all stress proteins will act in the manner disclosed in the specification. In effect, the Examiner is improperly requiring the Applicant to substantiate the presumptively correct teaching of the specification. This is in error. Even assuming that the rejection is proper, the Applicant submits that the skilled molecular biologist or immunologist, enlightened by the above-enumerated criteria contained in the present specification and the knowledge in the art, would be more than capable of routinely generating and using any and all HSPs in the present invention.

THE SKILLED ARTISAN HAS AMPLE GUIDANCE
FOR IDENTIFYING A POPULATION IN NEED OF THE INVENTION

Third, the Examiner alleges that the specification has not taught which members within a given population would be in need of the instant invention. Specifically, the Examiner states that "there is no art of record that teaches which members of the population are to receive cancer treatments or prevention medicaments because it is not known which members of the population will develop cancer."

In response, Applicant notes that what is known in the art need not be included, and is preferably omitted from, the specification. At the time this application was filed, it was well-known in the art that certain members of the population are predisposed to certain types of cancer and would thus be in need of the instant invention. Such individuals can be identified based on factors such as family history and environmental factors. Predisposition includes a high risk of melanoma as a result of exposure to the sun (see

Elwood, 1992, *World J. Surg.* 16(2):157-165; reference CS of the Supplemental Information Disclosure Statement) and a high risk of lung cancer as a result of exposure to asbestos (see Egilman and Reinert, 1996, *Am. J. Ind. Med.* 30(4):398-406; reference CT of the Supplemental Information Disclosure Statement).

Furthermore, aside from generally known environmental causes of high cancer risk, the art was brimming with knowledge about familial and environmental conditions that result in a heightened risk of cancer in an individual at the time the present application was filed. As support for the foregoing, the Examiner's attention is directed to references CU-CY of the Supplemental Information Disclosure Statement, which teach different types of cancer risk. For example, reference CU, a paper by Rozendall *et al.*, 1996, *Int. J. Cancer* 68(6):766-9, describes screening for a high risk of cervical cancer by detection of "high-risk human papillomavirus (HPV)" by PCR methodology. Even in the face of normal PAP smears, testing for high-risk HPV identified individuals with an increased risk of cervical cancer. Another publication, reference CV by Curley *et al.*, 1995, *Ann. Surg.* 222(3):375-80 at 380-83, describes identification and screening of more than 400 patients with chronic hepatitis B or C at high risk to develop hepatocellular cancer, and concludes that the risk of hepatocellular cancer in this population was 25%. Reference CW, a review article by Narod, 1995, Clin. Biochem. 28(4):367-72, indicates that with respect to hereditary predisposition to cancer, molecular methods of screening to identify individuals genetically at risk were available for a variety of diseases, including breast cancer, ovarian cancer, nonpolyposis colon cancer, Gardner syndrome (familial polyposis coli), neurofibromatosis, multiple endocrine neoplasia, and Von-Hippel Lindau disease. For example, reference CX, a publication by Peelen *et al.*, 1996, *Eur. J. Hum. Genet.* 4(4):225-30, describes the genetic make-up of 22 breast cancer families, concluding that while mutations in either BRCA1 or

BRCA2 confer a high risk of breast cancer, mutations in BRCA1 confer an additional risk of ovarian cancer. Finally, reference CY, a publication by Yanagi *et al.*, 1999, Leukemia 13(4):542-52, describes the Philadelphia chromosome or bcr/abl fusion gene as the hallmark of chronic myeloid leukemia (CML) and the gene's role as a prognostic marker during CML treatment.

The foregoing references merely exemplify the knowledge in the art at the time of filing the present application regarding high risk cancer populations, in whom the prevention of cancer is desirable. As stated above, an Applicant need not disclose what is commonly known in the art. It is well within the ability of the skilled medical professional, in consultation with the patient, to decide whether use of the claimed methods is desirable for that patient. Accordingly, the Examiner's allegation that the Applicant has not provided sufficient guidance for identifying suitable individuals in whom the prevention of cancer is desired is erroneous and should be withdrawn.

SAFETY IS NOT A CRITERION FOR PATENTABILITY

Additionally, Applicant addresses the Examiner's statement that "Although the administration of the vaccine in combination with the HSP may eliminate cancer, the overactivated immune state may eventually lead to other diseases such as autoimmune diseases." Office Action at 3. The Applicant reminds the Examiner that safety is not a criterion for patentability. ("Congress has not given the Patent and Trademark Office responsibility for protecting the public by refusing a patent for any device which may be dangerous to use. Safety is not a criterion for patentability." More specifically, "[w]here there is some degree of risk involved in using a claimed invention, such as for many pharmaceuticals, the Patent and Trademark Office does not have the authority to refuse a patent because it deems the risk to the user to be too great." *Ex Parte Drulard*, 223 USPQ

364, 366 (PTO Bd. App. 1983). Thus, Applicant maintains that a determination "whether such diseases [as autoimmune diseases] are or will likely develop as a result of the instant invention" (Office Action at 3) is not a prerequisite for patentability.

Also, Applicant respectfully points out that there is no reasonable basis for believing that autoimmune disease may result from carrying out the methods of the invention. Such allegations are mere speculation on the Examiner's part. In fact, art of record and additional references submitted herewith support a position contrary to that of the Examiner, *i.e.*, that administration of heat shock proteins does not cause autoimmune disease. The Examiner's attention is respectfully directed to Feng II, reference CP (made of record in revised form PTO-1449 filed on December 23, 2002), and references CZ and DA of the Supplemental Information Disclosure Statement, by Tamura *et al.*, 1997, *Science* 278:117-119 and Janetzki *et al.*, 2000, *Int. J. Cancer* 88:232-238, respectively (made of record in revised form PTO-1449 submitted concurrently herewith). Specifically, Feng II remarks, "In addition, repeated injection of these syngeneic tissue components [hsp70 and an enriched FS-IEF-derived preparation from a syngeneic naïve mouse liver] into BALB/c mice resulted in no apparent autoimmune phenomena." Feng II, page 251, first full paragraph. Similarly, Tamura *et al.* and Janetzki *et al.* observe a notable lack of autoimmune phenomena resulting from administration of heat shock proteins. *See* Tamura *et al.*, at page 119, last partial paragraph through page 120, first partial paragraph and Janetzki *et al.* at page 234, column 2, second full paragraph.

Accordingly, in view of the foregoing, Applicant respectfully submits that the Examiner's rejection of claims 4, 9, 13, 17, 21, 25-42, 44, 46-47, 82-91, and 93-99 is obviated and/or overcome and request that the rejection be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has maintained his rejection of claims 4, 9, 13, 27, 30, 33, 42, 44, 46, 82, 86, 90, 93, 94, 95, and 97 as anticipated by Chen *et al.*, 2002, *Cancer Res.* 60(4): 1035-1042 under 35 U.S.C. § 102(a). Paradoxically, while the Examiner acknowledges that the claims are directed to "a method of treating or preventing cancer comprising the administration of [1] a vaccine composition comprising a component that displays the antigenicity of a cancer cell and [2] a HSP [preparation] which does not display [the] immunogenicity of the vaccine component," (Office Action at 5, emphasis added), the Examiner insists that Chen *et al.*, a reference which discloses a single fusion protein consisting of a DNA vaccine which also happens to be an HSP preparation, allegedly anticipates the current claims. Applicant respectfully asserts that the Examiner has misconstrued the legal standard for anticipation and respectfully submits that Chen *et al.* does not anticipate the claims at issue.

The legal standard for anticipation is one of strict identity. Anticipation demands that a single prior art reference disclose all of the limitations of a claim. *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed. Cir. 2001). The Federal Circuit has repeatedly emphasized that for anticipation to abide, all the limitations of a claim must be met. *Id*; see also *Sandt Technology, Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d 1344 (Fed. Cir. 2001); *Rapoport v. Dement*, 254 F.3d 1053, 1057 (Fed. Cir. 2001). It is incumbent upon the examiner to identify wherein each and every element of the claimed invention is disclosed in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461, 1462 (Bd. Pat. App. & Int. 1990).

The Examiner has not identified every element of the claimed invention in Chen *et al.* As discussed above, Chen *et al.* discloses a single fusion protein. In contrast, in the claimed invention, the vaccine composition and the HSP preparation cannot be the same substance, since the vaccine composition and the HSP preparation do not display the same immunogenicity. In other words, the plain language of the claims requires administration of at least two distinct molecules: (1) a component which displays the antigenicity of a cancer cell, *i.e.*, the vaccine composition, and (2) a preparation which does not display the immunogenicity of the component, *i.e.*, the heat shock protein preparation. Chen *et al.* describes only one molecule, a fusion protein. Chen *et al.* cannot satisfy each and every limitation of the claims. Applicants respectfully submit that the Examiner's construing of the term "heat shock protein preparation," which has been amended to recite "purified heat shock protein preparation," as being a portion of a molecule that is the vaccine composition component is a tortuous, unreasonable reading of the claim language that is contrary to its plain meaning.

While the Examiner may be correct that Chen *et al.* discloses a fusion protein wherein "the E7 antigenic portion and the HSP70 portion" "have different and distinct immunogenic determinants," that is not the test of anticipation. The Applicant is not claiming a single component with different and distinct immunogenic determinants. Applicant is claiming a method comprising the administration of at least two substances, one of which comprises a component that displays the antigenicity of a cancer cell, and one of which is purified and which does not display the immunogenicity of the component. Clearly, the two substances are distinct and are not portions of the same molecule. This would be abundantly clear to one skilled in the art. Anticipation is a rigorous standard which requires

strict identity and fulfillment of each and every limitation of the claims. That standard has not been met here.

In sum, since the HSP preparation of Chen *et al.* necessarily displays the immunogenicity of the component of the vaccine since it is the component, the Chen *et al.* fusion protein cannot anticipate the present claims. Accordingly, in view of the foregoing, Applicant submits that the rejection is in error, and respectfully requests its withdrawal.

REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 4, 9, 33, 42, 44, 46, 82, 86, 90, 94, 95 and 97 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chen *et al.* In addition, claims 4, 9, 13, 17, 21, 25-42, 46, 82, 83, 86, 90, 93, 94, 95, and 97 are rejected under 35 U.SC § 103 as allegedly unpatentable over Yang *et al.* in view of either Suzue *et al.* or Chen *et al.* Applicant disagrees with the Examiner for the following reasons.

Prior art references may indeed be combined to render an invention obvious under 35 U.S.C. § 103, however, the teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). The teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 173 F.3d 994, 999 (Fed. Cir. 1999).

The Federal Circuit has expressly indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggests combining the asserted references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). More specifically, the motivation to combine references originate

from one of three sources: the nature of the problem to be solved, the teachings of the prior art, or the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Consequently, the reason or suggestion in the art for carrying out the invention, must originate from a source other than the knowledge learned from the Applicant's disclosure (*In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)), and care must be exercised not to use the Applicant's disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985).

Claims 4, 9, 33, 42, 44, 46, 82, 86, 90, 94, 95 and 97 have been rejected as allegedly obvious over Chen *et al.* The Examiner acknowledges that Chen *et al.* does not teach the administration of the HSP before or after the administration of the vaccine. The Examiner maintains however, that it would have been *prima facie* obvious to one of skill in the art to administer the HSP and the vaccine on the same day and concurrently.

In response, Applicant reiterates that Chen *et al.* only teaches the administration of an HSP-vaccine fusion protein, which is an HSP preparation in which the HSP molecule displays the immunogenicity of the vaccine component, *i.e.*, the antigenicity of the papillomavirus E7 antigen. There is no suggestion in Chen *et al.* of administering a DNA vaccine and an HSP in which the vaccine and HSP are separate molecules. As explained above, there is no suggestion in Chen *et al.* of administering an HSP preparation that does not display the antigenicity of the vaccine component. Thus, the claimed invention is non-obvious over Chen *et al.*

In response to the rejection of claims 4, 9, 13, 17, 21, 25-42, 46, 82, 83, 86, 90, 93, 94, 95, and 97, over Yang *et al.* in view of Suzue *et al.* or Chen *et al.*, Applicant respectfully disagrees that the above combined teachings render the presently claimed invention obvious.

The Examiner has not come forth with any objective evidence of record in support of his obviousness rejection. The Examiner states that the claimed invention would be obvious in light of the fact that 1) "use of tumor associated antigens was well known and established in the art as a means to generate an immune response to an antigen found on tumor cells" and 2) "the use of HSP as an immune regulator or stimulator was also well known and practiced in the art at the time of filing." Office Action at 6. The Examiner concludes that "It is therefore obvious to combine the teachings of the two methods to develop a method of treating cancer because it was already known in the art to practice either invention separately." Office Action at 6. The Examiner has pointed to no teaching of record which evidences a motivation to combine Yang *et al.* with the teaching of Suzue *et al.* or Chen *et al.* The Examiner's alleged motivation for combining the references does not satisfy the legal requirement for being "clear and particular." It is Applicant's disclosure which teaches the administration of (i) a vaccine component which displays the antigenicity of a cancer cell, and (ii) a heat shock protein preparation which does not display the immunogenicity of the component.

Even assuming arguendo that the skilled artisan had motivation to combine Yang *et al.* with either Chen *et al.* or Suzue *et al.*, such combined teachings would not render the claimed invention obvious. Yang *et al.* teaches that administration of a gene-modified, dendritic cell-based vaccine is more effective than a naked DNA-based vaccine at eliciting anti-tumor immunity in therapeutic and prophylactic models. Yang *et al.* does not teach the administration of any hsp preparation, must less an hsp preparation which does not display the immunogenicity of the component that displays the antigenicity of a cancer cell.

Suzue *et al.* does not effectively bridge the gap left by Yang *et al.* Suzue *et al.*, only teaches the use of a fusion protein containing a large fragment of ovalbumin

covalently linked to mycobacterial hsp70 to elicit a CD8 cytotoxic T lymphocyte response. Thus, Suzue *et al.*, like Chen *et al.* discussed above, only teaches an hsp preparation which displays the immunogenicity of the vaccine since the fusion protein is the vaccine. Thus, an examination of the teaching of Yang *et al.* combined with the teaching of either Suzue *et al.* or Chen *et al.*, does not reveal every element of the claimed invention.

In sum, the Examiner has not met his burden of setting forth a motivation to combine Yang *et al.* with either Chen *et al.* or Suzue *et al.* to arrive at the methods claimed herein and even if combined, the foregoing references do not teach all the limitations of the claims. Accordingly, in view of the foregoing, Applicant submits that the rejection is in error, and respectfully requests its withdrawal.

THE INDEFINITENESS REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claim 93-99 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner states that claims 93-99 are indefinite in their recitation of "effective amount" since it is unclear what amount is intended to accomplish the desired task. Office Action at page 6. Applicant respectfully asserts that the term "effective amount" as used in claims 93-99 is definite for the reasons set forth below.

The CCPA has articulated the legal standard for evaluating whether the phrase "an effective amount" is definite. A proper definiteness inquiry turns on "whether or not one skilled in the art could determine specific values for the [effective] amount based on the disclosure. See *In re Mattison*, 509 F.2d 593, 184 USPQ 484 (CCPA 1975)." MPEP 2173.05(c)(III). Thus, a claim may be indefinite if it fails to state the function which is to be achieved by the "effective amount." See *In re Frederikson*, 213 F.2d 547 (CCPA 1954)(holding the phrase 'an effective amount' is on its face indefinite since it fails to state

the function which is to be rendered effective.) Additionally, "more recent cases have tended to accept a limitation such as 'an effective amount' as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim" citing In *Ex Parte Skuballa*, 12 USPQ2d 1570 (BPI 1989)(holding that a "pharmaceutical composition claim which recited an 'effective amount of a compound of claim 1' without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses would be effected.") MPEP 2173.05(c)(III).

Applicant asserts that the claim phrase "effective amount" as used in claims 93-99 is definite. Preliminarily, claims 93-99 set forth the function which is to be achieved, that is, "to induce or increase an immune response in the subject to the component." Second, the specification provides ample guidance as to specific dosages and factors to guide one of skill in the art in making a determination of what is an effective amount. The Examiner's attention is respectfully directed to page 34, line 7 through line 23 of the specification as filed. Therein, the specification sets forth specific dosages of HSP preparation that may be used in conjunction with the instant invention. Specifically, the HSP preparation can range from 0.1 to 1000 μg per administration. Additionally, specific ranges are set forth for particular HSPs, "preferred amounts of gp96 or hsp70 are in the range of 10 to 600 μg per administration and 0.1 to 10 μg if the HSP preparation is administered intradermally. For hsp90, the preferred amounts are about 50 to 1000 μg per administration, and about 5 to 50 μg for intradermal administration." Specification, page 34, lines 17-23. In addition, mere routine experimentation, well within the skill of one skilled in the art, can be used to determine the appropriate dosage.

The specification also sets forth numerous factors which may guide a person of skill in the art in determining an "effective amount". Specifically, the specification teaches that the dosage of HSP preparation to be administered depends on 1) the condition and size of the subject being treated; 2) the amount of vaccine composition administered; 3) the frequency of treatment; and 4) the route of administration. Specification, page 34, lines 7-12. The specification also teaches that "regimens for continuing therapy, including site, dose and frequency may be guided by initial response and clinical judgment." Specification, page 34, lines 12-14.

Thus, "effective amount" as used in the claims, in view of the specification as filed and the knowledge of one of skill in the art, is not indefinite.

In addition, the Examiner has rejected claims 93-99 as allegedly indefinite for recitation of the term "increase" since there is allegedly "no comparison to a base level." Office Action at page 7. Applicant respectfully submits that "increase," as the term is used in claims 93-99, is definite.

Definiteness turns on whether one of skill in the relevant art would understand the bounds of a claim when read in light of the specification. *See Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986).

The term "increase" was not intended to be read in isolation, but instead in light of the specification as a whole. The specification as filed provides ample guidance for interpreting the term "increase" as used in claims 93-99. Applicant directs the Examiner's attention to section 5.5 of the specification, titled "Determination of Immunogenicity of Vaccines After HSP Treatment" wherein the Applicant teaches various methods of measuring the immune response produced by the methods of the invention. Notably, Applicant begins the section by stating "the *production or increase in immunogenicity of a*

vaccine that is used with the HSP preparation of the invention can be assessed using various methods well known in the art." Specification at page 39, lines 30-33 (emphasis added). One of skill in the art would readily understand that the "increased" immune response is increased relative to the immune response produced by administration of the vaccine composition alone. In other words, the allegedly omitted base line is explicitly defined by the immune response generated by administration of the vaccine composition in the absence of the HSP preparation of the claimed invention.

In light of the teaching contained in the specification, one of skill in the art would be reasonably apprised of the meaning of the term "increase" as used in claims 93-99. Therefore the indefiniteness rejection is in error and should be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendment and remarks into the file history of the above-identified application. Applicant believes that each ground of rejection has been successfully overcome, and that all pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the application, are respectfully requested.

Respectfully submitted,

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